9 Enlightened Minds and Stone Disease

Introduction

The eighteenth century is remarkable for the development of our modern notions such as science and technology in an increasingly sophisticated and mechanical world; it is the age of adoption of the humanistic precepts of the seventeenth century coupled with awareness that via experiment, knowledge could transcend even classic learning. There were great expectations for man's potential but also great recklessness in man's ability to wage war with the French King Louis XVI getting beheaded on January 21, 1793, and the rise of Napoleon Bonaparte just 5 years later. As with all of our previous chapters, there is no absolutely defining moment that identifies the Enlightenment, but the zeitgeist (spirit, Herder 1769) is best summarized by Voltaire, the literary master. The Enlightenment also saw the institutionalization of knowledge by the creation of encyclopedias.

The French *Encyclopédie*, *ou Dictionnaire raisonnè des sciences*, *des arts*, *et des métiers* of Denis Diderot (1713–1783) and Jean-Baptiste le Rond d'Alembert (1717–1783) epitomizes this period of human accomplishment. The *Encyclopédie* was first released in Paris in 1751 and sold more than 4,000 copies [1]. It was written for the average intelligent person and their families. Medicine figured prominently in the writing which was classified in the physical sciences. There were 139 handpicked contributors to the *Encyclopédie*, and the medical giants mostly from the continent came forth. The sections on the kidney and stone disease were at the forefront of the times [1]. "*The kidneys are 2 paired extraperitoneal organs*. *They are located between the lumbar ribs and muscles*, *on the right and left side of the spine*, *and are embedded in a fatty environment…The kidneys are the most dense visceral organs*, *move with respiration*, *and the lower pole of the right is below that of the left side*. *In the kidney*, *one distinguishes a cortical part*, *which is yellow*, *soft*, *and highly vascularized*, *and a medullary part*, *which is more dense*, *whiter*, *and more consistent*, *made of lobules*, *which in adult humans are joined together*. *Here*, *we recognize pyramidal structures of different size*, *in which are columns consisting mainly of tubular conduits*" [2]. This is a modern method of description which could be read in any current textbook. They try to keep current by proceeding to physiology and speculation: "*For Malpighi*, *the kidney was a glandular organ made by small arteries forcing their fluids into a spherical cavity continuous with a small urinary conduit*. *The most colored part of the blood is separated in these glands*" [2]. This represented the microscopic findings of Malpighi. It goes far beyond the hypotheses of van Beverwijck and incorporates all of the newest scientific findings. He continues "*It cannot be doubted that urine is brought to the kidney by arteries*, *is poured in the urinary conduits and received into the ureter*." He continues "*An identical road is covered by lithic matter or the calculous clot preceding stone formation*" [2].

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The Enlightenment would also see the rise of philosophers: Francis Bacon, Burke, Condorcet, Hobbes, Home, Hume, Kant, Locke, Rousseau, Adam Smith, Baruch Spinoza, and Wolff. The writers included the following: Boswell, Gibbon, von Goethe, de Gouges, Hobbes, Voltaire, and Mary Wollstonecraft. The political thought leaders included Boehmer, Burke, Condorcet, Benjamin Franklin, Alexander Hamilton, Jefferson, Locke, Madison, Montesquieu, and Paine. The natural philosophers deserve special attention and include d'Alembert, Berkeley, Buffon, Franklin, Hooke, Lavoisier, Leibniz, von Linné (Linnaeus), Isaac Newton, and Volta. The literal outpouring of knowledge was certainly not limited to these giants; this was also the time of Mozart and James Cook and the Reverend William Paley who developed his influential rationalization of religion. But it also ushered in the first outspoken atheist in Baron d'Holbach and the most ostracized philosophy of Spinoza (which quite possibly best summarizes our current brain physiology of consciousness) who was vilified by all major religious faiths.

Stone Disease and the New Medicine

From the beginnings of Leyden (Leiden) as a famed medical school came a little known Scottish physician Pitcairne. He was to leave Leiden opening the way to Boerhaave and returned to Edinburgh and influenced the minds of Reverend Stephen Hales and Dr. Robert Whytt. Edinburgh would gradually rise to become the leading light of medical knowledge as the Scottish Enlightenment would also eclipse the Western world. Stone disease was on the rise, and certain communities noted especially high prevalence rates, such as Norwich in England. William Cheselden (1688–1752) became the surgeon at St. Thomas's Hospital in London and achieved fame as a lithotomist. But first a digression is necessary to Joseph Priestley (1733–1804), an enlightened mind if ever there was one. His intelligence was applied to many areas but we are interested in his notion of Phlogiston and fixed air. He published his work "*Consideration on the Doctrine of Phlogiston and The Decomposition of Water*" in 1796 [3]. He literally was taking some of the notions of van Helmont and adding to them. Antoine Lavoisier (1743–1794) would have major controversial disagreements with the experimental observations of Priestley, and even some of Priestley's devoted friends such as Dr. Erasmus Darwin fellow member of the Lunar Society would side with Lavoisier [4]. Yet, carbon dioxide as we now know it would become the basis for modern chemistry, especially organic chemistry.

Others would pick up the thread of fixed gas and begin to investigate common substances, especially calculi which were beginning to get collected by surgeons. The Reverend Stephen Hales (1677–1761) was one of those investigators (Fig. 9.1d). Hales was born at Bekesbourne near Canterbury Kent on September 17, 1677. Hales matriculated at Cambridge in the spring of 1696 and was elected as fellow at St. Benet College in 1703. He worked on plant and animal physiology with his lifelong friend Stukeley and was interested in medicine by interactions with Pitcairne at Edinburgh. He was enamored with chemistry and repeated the experiments of Boyle [5]. He read and digested Newtonian physics. He left Cambridge and became a minister of the parish of Teddington in the County of Middlesex in 1709. His mind was curious and probing, and being a minister, he had ample time left for experimentation. Hales began a series of experiments in physiology and chemistry, and he began to send his writings to the Royal Society: "*The Rev: Mr Hales informed ye President that he had lately made a new experiment upon the effect of ye Sun's warmth in raising sap n trees. Mr Hales was desired to prosecute these experiments and had thanks for communicating the first essay*" [5]. This was logged into the Royal Society Journal Book in 1718. These studies were eventually published in a book *Vegetable Staticks*. He followed with a series of experiments that made him famous on blood pressure determination, but he became engrossed in stone disease [6]. He may have been following up on some of the investigations of Boyle, but he was well aware

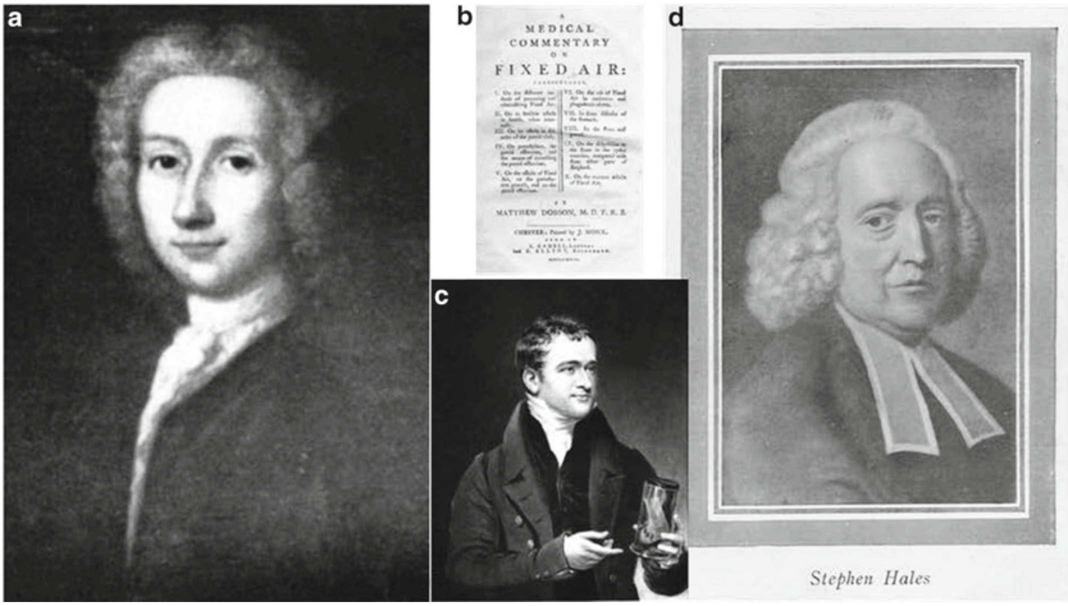

Fig. 9.1 (**a**) Robert Whytt. (**b**) The book by Matthew Dobson "A Medical Commentary on Fixed Air." His only known portrait was accidentally destroyed by house staff junior surgeons in Liverpool. (**c**) Karl Wilhelm Scheele. (**d**) The Reverend Stephen Hales

that "distemper of the stone" was a common condition throughout England [5]. He resolved to do some chemistry on the stone in search of a method of dissolving these concretions. He even invented a double-lumen catheter to deliver his solutions in canine (dog) experiments.

Hales had an amazing quality for grasping complex problems and thinking them through and, even with little information or experience, would intuit solutions that eventually would become accepted. Not only did he develop a double-lumen catheter; he also devised an ingenious forceps device that could extract urethral stones that would eventually get rediscovered by the likes of John Hunter: "*I cut off the lower end of a straight Catheter for a Stillet or Forceps to pass thro*'; *the lower end of the Forceps was divided into two Springs like Tweezers who Ends were turned a little inwards*" [6]. His writings and investigations on calculus disease were eventually published with his sentinel work on blood pressure. In 1739 he was awarded the Royal Society's Copley Medal for this work. In order to develop a solvent for stones, he needed to understand the nature of the stones themselves. He subjected bladder stones to a blowpipe and tried to understand their chemical composition [7]. He used preparations of nitric acid and sulfuric acid and measured their responses. At one point he wrote, "*I suspect that the principal Cause of the first beginning of the Growth of Gravel in the Kidnies*, *is owing to the horizontal Posture we are in when we lay in Bed*: *In which Posture one of the Kidnies being lower than the Bladder when we lay on one Side*, *and both the Kidnies when we lay on our Back*; *the Pelvis or Cavity of the Kidnies becomes thereby the Sink for the tartarine Parts of the Urine to settle in*" (228) [7]. He uses his understanding of physics to speculate further: "*Progress of the Urine being in some degree retarded*, *it has more time to deposite its Tartar in those small Ducts in the Papillae*, *where it is thought the first minute Beginnings of Gravel are usually formed*; *it being in Dissections found there*" [7] (Randall's plaques and the modern hypothesis of Dr. Marshall Stoller). Later in his life, he became involved in the nefarious incident by the government in purchasing Joanna

Stephens' medicine. He wrote "*An Account of Some Experiments and Observations on Mrs Stephens' Medicines for the Stone*." in 1740 [8].

Robert Whytt is another forgotten player on the stage of medicine (Fig. 9.1a). On October 19, 1903, a disciple of William Osler read a tribute to the history of this physician at the Johns Hopkins Hospital Historical Club [9]. Whytt trained at the new medical school in Edinburgh between 1730 and 1734. He went to London and worked with Cheselden. He went to Paris and attended the clinics at La Charite and the Hôtel Dieu. He then went to Leiden to listen to the ancient professor Boerhaave and his heir Albinus. He took his medical degree from Rheims which was commonly done by Brits [9]. In 1747 he was chosen as the chair of the theory of medicine at his alma mater which he then held for the rest of his life. In 1743 he published his "Edinburgh Medical Essays." In this work, he presented a paper "On the Virtues of Lime-Water in the Cure of Stone." This paper and work was triggered also by the controversial medical cure of Mrs. Stephens that had attracted Hales. Whytt thought that limewater might be a better delivery agent and began to prescribe it to his stone patients by 1741. He seems to have had a good deal of success and usually mixed this with soap. Whytt's treatment was to give an ounce of Alicant soap and about three pints of limewater daily. The alkalinity of this solution probably had some effect on uric acid stones that predominated in his patient population. He went on to perform numerous experiments ex vivo with his limewater and did honestly note that it did not perform as a universal solvent, similar to the findings of Hales. He investigated numerous other water sources and discusses some controversial aspects of stone dissolution at odds with Dr. Alston. He expanded his stone studies and published them in 1750. His work probably triggered the interest in Black to investigate calcareous earths and fixed air. Whytt became suddenly ill and died in 1766. His collected works were published by his son and Sir John Pringle in 1768 [10]. Seller summarized the sad loss of this accomplished individual by stating "*In short, Whytt, though of an ardent temper, really was a man of well balanced feelings, earnest after truth, not unsolicitious of fame, whole all the sentiments he expresses indicate a benevolent turn of mind, full of love to mankind, and a determination, at any cost to himself, to fulfill the duties of his station*" [9].

Protochemistry

Karl Wilhelm Scheele (1742–1786) has been referred to as "hard-luck Scheele" by Isaac Asimov because even though he made many discoveries before others such as Priestley, Davy, and Lavoisier, he seldom got credit because he did not publish timely or in places that were widely read (Fig. 9.1c) [11]. Scheele was born in Stralsund, Sweden, on December 9, 1742 [12]. He came from a modest background and apprenticed as a pharmacist in Gothenburg for 8 years. He then worked as a pharmacist in Stockholm, Uppsala, and Köping during his life. He also became profoundly interested in chemistry and performed many experiments. In 1776 Scheele turned his inquiring mind to urinary tract calculi [13]. He revealed that the main component of a bladder stone was a substance that was barely soluble in cold water but was an acid that turned litmus paper red. This substance dissolved in alkali and precipitated in acids. He dissolved this substance in hot nitric acid which he was able to isolate following evaporation which was a pinkish crimson color. He heated this in a flame, and it gave an odor like prussic acid, ammonia, or burnt horn [13]. He described these revolutionary findings at the Academy of Sciences in Stockholm. He named his substance lithic acid, and he stated that it was the major component of all stones.

Andreas S. Marggraf (1709–1782) is similar to Scheele except the fact that his writings were presented in Berlin and written in French. He also was the son of a pharmacist and became an adept chemist [14]. Like Scheele he devoted himself to new chemical methods. He attended medical school for 1 year in 1725 but became increasingly focused on chemistry. He simplified and explained the phenomenon of phosphorus in the urine and developed the chemistry of

Fig. 9.2 Rare colored rendering of Andreas Sigismund Marggraf (1709–1782)

phosphoric acid. Marggraf also developed a colorimetric analysis of various forms of phosphates. He is the first person to chemically note that there are different types of urinary stones based on composition. Berzelius confirmed these findings and those of Scheele. Marggraf's collected works were eventually published as *Chymische Schriffen* in 1766 [15]. Marggraf's contributions are typically overshadowed by the work of Scheele and the founders of chemistry, but his contributions were crucial; there is one known likeness image of him, a simple watercolor (Fig. 9.2).

Matthew Dobson, M.D., F.R.S.

Matthew Dobson (1732–1784) could almost be seen as the opposite of Reverend Stephen Hales. Dobson was born in Yorkshire, was the son of a Nonconformist minister, and was expected to follow in his father's footsteps. He, however, discovered medicine as a career within Edinburgh where he graduated in 1756. He developed a wide range of interests and was soon experimenting on many areas of physiology and medicine. He began his clinical practice in Liverpool in 1762 and became one of the founding physicians at the Liverpool Infirmary in 1770. He became interested in urinary stone disease and corresponded widely with the Royal Society and published in the Philosophical Transactions. Matthew Dobson first reported upon a statistical inquiry on the incidence of stone disease in various parts of England. The number of patients admitted to the Norwich infirmary was 30 times higher than those admitted to Cambridge Hospital. In Worcester, Hereford, and Exeter hospitals, there was 1 stone patient among 394 admissions. In northeast England including Newcastle, York, Leeds, and Manchester, the ratio was 1/420. In Liverpool, Chester, Shrewsbury, and North Wales, it was 1/3,223. He concluded that stone disease was more common in the "Cyder" districts and that hard water prevents rather than promotes the formation of stone disease. Quite the unexpected finding! He also began to investigate the ability of alkaline soap and limewater to aid in the treatment of stone disease, but unlike Whytt, he was significantly less impressed and noted it did not help in some cases of stone disease. He wrote his treatise "A Medical Commentary on Fixed Air" in 1779 (Fig. 9.1b).

In this work, it is Chaps. 8 and 9 that attract our interest. Most of the work is a series of experiments and clinical observations. Chapter 8 is called "In the stone and gravel." Chapter 9 is called "On the disposition of the stone in the cyder counties, compared with some other parts of England." In the introduction of this book, he gives credit to his sources prior to his experiments: "*…we find also*, *from the experiments of Dr. Hales*, *Sir John Pringle*, *Dr. McBride*, *and others*, *that Fixed Air enters very universally into the composition of animal substances*." He reviews the findings of virtually all pertinent information to this time including the works of Priestley, Lavoisier, van Helmont, Hoffman, Cavendish, Lane, Bewley, and Venel. He begins Chap. 8 with the comment "*An accurate and ingenious* *philosopher, the Hon. Henry Cavendish, has pointed out, by a connected train of experiments, that calcareous earths are made soluble in water, by being united with more than their natural proportion of Fixed Air*" (128–29). He moves onto some experiments but returns to the thesis "*This doctrine of the solution of calcareous earths, naturally suggested the idea of the solubility of the human calculus while yet in the bladder, by the regular and continued use of Fixed Air*." He is trying to define the notion of supersaturation of solutes with an interaction of carbon dioxide. He does not know about the conversion by the kidney into bicarbonate ions and the buffering effects of citrate, but he is getting remarkably close to modern urine biochemistry. He quotes a study from the eminent physician and ethicist who experimented upon a test subject, Dr. Percival: "*A young gentleman…has, at my desire, taken large quantities of mephitic water daily, during the space of a fortnight. And whilst he continued this course, his urine was strongly impregnated with Fixed Air, as appear'd from the precipitation which it produced in lime-water; from the bubble which it copiously emitted when placed under the receiver of an air-pump; and from the solution of several urinary stones, which were immersed in it*" (132–33).

Sampson Perry, Surgeon

Towards the end of the eighteenth century, a surgeon wrote a treatise entitled "*A Disquisition of the Stone and Gravel; with Strictures on the Gout, When combined with those Disorders*." This was Sampson Perry who published his textbook in 1772 from London and dedicated it to the Royal College of Physicians. He was born in 1747 in Aston and practiced surgery in London through the 1760s. He joined the East Middlesex Militia in 1765 and became a captain during the American War of Independence. He was twice honored by King George III. He became a newspaper owner/editor for the *Argus* that evolved increasingly radical political views and supported the French Revolution [16]. He was contemporaneous with other liberal intellectuals including James Parkinson and Thomas Paine.

His textbook *A Disquisition of the Stone* sold well, and he came out with a seventh edition by 1785 [17]. He begins his dedication by stating candidly "*In respect to that part, which treats of the discovery of a cure for the stone, I flatter myself the world will do me the justice to view it in its proper light, particularly as I have not dealt in conjectures, but in matters of fact*" [17]. He continues in his preface by stating that he is a surgeon and will bring a surgeon's perspective to his discussions. He has two postulates that he puts forth early: first that stones form in the kidney and are conveyed to the bladder and second that once in the bladder, they can grow and enlarge which then causes troubles [17]. He also attacks the widespread attempts of the previous authors of the Enlightenment by showing that it is very difficult to dissolve stones with any solvents in humans. His first seven chapters concentrate on stone disease, and in the final chapter, he discusses gout. Perry discusses some of the unique properties of urine: "*That the urine is an elementary fluid, or rather made up of elements, is evidently demonstrated by the frequent experiments made on it by chymists, from which they extract an insipid lymph, a volatile spirit, an acid saline matter, some oil, and a fixed earth*" (9). He builds to a crescendo and names the causation of stone disease in Chap. 3, Section "Physicians and Suffering." He states that "*human calculi are of very different degrees of density and cohesion; some being so loose and friable as to crumble to pieces between the fingers, while others have been taken from the body, of such a compact and flinty nature, as to strike fire in collision with steel…*" (25). In Sect. 2, he discusses the suppositions of others as to causality, and he specifically addresses the drinking of water, the climate, and the food that are all implicated in stone disease. In Sect. 3, he discusses the microscopic characteristics specific to the kidney and uses the measurements of Lieuenhock [Leeuwenhoek] with tubule diameters of 1/80,000 of an inch to begin to build to his hypothesis that these small tubules represent the site of stone formation [17]. He next describes some ingenious experiments where he places human stones in urine of non-stone formers and stone formers to measure change in mass.

In Chap. 3, Section "Physicians and Suffering," he announces what he believes is the cause of all stone formation he titled "Of the Real Cause of the Stone" [17]. He believes that the elemental particles that produce the stone separate from the blood in the tubules of the kidney, and he names them "*primary particles of stone*" (48). Once the primary particles are separated from the blood in the tubules of the kidney, "*those primary particles so as to become a nucleus of the stone*: *for*, *from the second experiment of the same section we find*, *that when once a nucleus exists in the body*, *it collects by its attractive power*, *the particles abut its surface*, *and thereby accumulates continually*" (48). He believes all the centers of stones are these nuclei and that they all form in the kidney. Bladder stones form from stones that began in the tubules of the kidneys and have passed down the ureters to the bladder. This is also a remarkably modern concept. He is not the chemist that Priestley, Hales, Scheele, or Marggraf is, so he does not know that stones are formed from different chemical components, but he essentially is getting to the modern notions of nucleation, fixed particle retention, and supersaturation. He would live the remainder of his life running from his radical politics. First warrants for his arrest in England forced him to flee to Paris at the height of the "reign of terror." He was imprisoned in Paris for 401 days and was sentenced to the guillotine but escaped with a rather remarkable stroke of luck and daring. On returning to England, he was promptly arrested again and imprisoned for 8 more years which he spent writing a history of the French Revolution [16]. Almost no one credits his writings as a physician in the modern era.

Discussion

The eighteenth century saw the rise of scientific inquiry and the acceptance of the Industrial Revolution by the Western world. Sir Isaac Newton proved beyond a shadow of anyone's doubt that applied mathematics and science was a potent combination and the world shuddered. But Newton was always a reclusive sort and began to suffer with bladder stones, obstruction, and gross hematuria: "*In August*, *1724*, *the presence of a dreaded disease declared itself by his voiding without any pain*, *a stone*, *about the size of a pea*, *which passed in two pieces*" [18]. His health continued to decline, and he resigned his post at the Royal Society secondary to bouts with painful gout by 1725. On March 4, 1727, Newton experienced severe pains and his physician diagnosed a bladder stone: "*The pain rose to such a height that the bed under him*, *and every room shook with his agony*, *the wonder of those that were present*" [19]. The great mind of his time would stand no more on the shoulders of giants.

Bartolomeo Eustachio's (c.1500–1574) illustrations were lost until rediscovered and published in 1714 by Lancisi [20]. They revealed an unparalleled degree of observation by this great anatomist, including the renal tubules that had been rediscovered by Bellini [21]. Marcello Malpighi (1628–1694) extended these observations with microscopic examination of the kidneys and the first description of the glomerulus in his *De Renibus* in 1666 [22]. He hypothesized that "*For the most part the abnormalities appearing in the urine spring from disease of the blood coming to the kidneys*, *and particularly those hereditary diseases whose diathesis is not developed in the structure of the kidney*, *but is in the blood*." Malpighi would hypothesize that stones originally formed in the renal tubules and resulted in progressive renal damage: "*Now it frequently happen that small stones are held in these membranous ducts and are enlarged by the accretion of tartar*, *so that they injure the delicate membrane of the vessels and consequently the flesh of the kidneys is often observed to be destroyed*" [23]. The child prodigy and gifted pupil of Malpighi's heir Valsalva, Giovanni Battista Morgagni (1682–1771) would take the next logical steps [24]. He studied medicine at age 15 and assumed the chair of anatomy at Padua at age 33. In his towering work *The Seats and Causes of Diseases Investigated by Anatomy* in 1761, he detailed observations on autopsy of patients with stone disease. In Book II, letter L, article 15, he states "*But as we see it so often happen*, *that one kidney not secreting*, *or not emitting urine*, *by reason of its being corrupted*, *on account of obstructing calculi*, *is supplied by the other*, *and* *that this is confirmed by the very increase of it*." He articulately describes compensatory hypertrophy of the contralateral kidney. Morgagni specifically alludes to this hypothesis noting a case of infant stone disease: "*And there are urines which deposit these particles sooner, and more readily*, [*Brendelius*] *does not at all doubt, where he mentions the cases of two infants; one but just two days old, and the other about eight; who not only dischrg'd calculi before death, but had calculi found with them when dead*" [25]. He continues "*In summer the calculous matter is much less diluted by the watery matter, which then goes off, through the skin, in a very considerable portion: and this seem to me another reason why, if it is in our power to choose, the excision of the calculus should be put off from autumn to spring, rather than from the spring to autumn*" [25]. This is a remarkably modern insight; it presages the seasonal incidence of stone disease and presents the etiologic reason for "stone belts" that has to do with insensible fluid loss and dehydration. He concludes in Book III, letter XLII, article 20, with one of the first descriptions of stone formation upon a foreign body: "*a country girl…died in her fourteenth year. For having introc'd a brass hair-bodkin, notwithstanding it was bent in the middle, very high into the urethra,…she was silent as to the true cause of the pains. For even the bodkin could not be extracted, by reason of a calculus that was form'd upon it. But the ureters, and the kidnies themselves, were in a very bad condition indeed*" [25].

John Bostock (1773–1846) was a physician and trained apothecary who also studied medicine in Edinburgh and Leiden then became a junior physician with Matthew Dobson in Liverpool [26]. He worked with Joseph Priestley and became a transitional figure with many of the early modern founders of stone chemistry in London. He was contemporaneous to Wollaston, Marcet, and Michael Faraday. He published on the chemistry of urine in 1805 and 1813, and he followed these with autopsy findings later in the nineteenth century [27]. He influenced William Prout and was a mentor to Richard Bright, all of whom we'll meet in "Founding Fathers" chapter. The shadows of the future of medicine would come hauntingly quick from the brilliant mind of a physician doomed to shine bright and burn out like a supernova, Marie-Francois Xavier Bichat. He was a young French anatomist who wrote four books with limitless possibility for medical science and died of tuberculosis on July 22, 1802, at the age of just thirty [28]. Bichat stated "*you may take notes for twenty years, from morning to night at the bedside of the sick, upon the diseases of the viscera, and all will be to you only a confusion of symptoms, - a train of incoherent phenomena. Open a few bodies, the obscurity will disappear*" [29]. We began using Francois-Marie Arouet de Voltaire as the eponymous figure of the Enlightenment. In a little discussed work from this prolific writer (over 2,000 books and pamphlets), he wrote "Extreme." He chose medicine as a metaphor to man's progress: "*The first man who at the right moment bled and purged a sufferer from an apoplectic fit; the first man who thought of plunging a knife into the bladder in order to extract a stone, and of closing the wound again; the first man who knew how to stop gangrene in a part of the body, were without a doubt almost divine persons, and did not resemble Moliere's doctors*" [30]. The Enlightenment came to a close, and Voltaire said in *Candide*, "*The dread of depriving man of some false liberty, robbing virtue of its merit, and relieving crime of its horror, has at times alarmed tender souls; but as soon as they were enlightened they returned to this great truth, that all things are enchained and necessary*" [31].

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